I. GENERAL INFORMATION

A. File Number

NADA 138-952

B. Sponsor

Elanco Products Company
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

C. Proprietary Name

MAXIBAN®

D. Established Name

Narasin and Nicarbazin Type A Article

E. Dosage Form

A 1:1 combination of narasin and nicarbazin is supplied as a Type A medicated article in 50-pound bags for inclusion into broiler feeds. A premix concentration of 36 g/lb (80 g/kg) of each narasin and nicarbazin is provided.

F. Dispensing Status

OTC

G. Dosage Regimen

Narasin and nicarbazin (from MAXIBAN®) at concentrations ranging from 27/27 g/ton to 45/45 g/ton of each in finished feeds.

H. Route of Administration

Oral administration via the feed.

I. Indication

For the prevention of coccidiosis in broiler chickens caused by *E. necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*.

II. EFFECTIVENESS

A. Introduction

Narasin Premix is approved (21 CFR § 558.363) for incorporation into the rations of broiler chickens at levels of 54-72 g narasin/ton for the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acerrulina*, *E. brunetti*, *E. mivati*, and *E. maxima*. Nicarbazin is also approved (21 CFR § 558.366) for incorporation into broiler chicken rations at 113.5 g/ton as an aid in prevention of outbreaks of cecal (*Eimeria tenella*) and intestinal (*Eimeria acerrulina*, *E. maxima*, *E. necatrix* and *E. brunetti*) coccidiosis in chickens. Experiments have shown that

with the combination narasin plus nicarbazin superior control of all species of coccidia is attained at reduced dosages of each drug and at generally reduced net dosages.

Extensive tests have shown that a 1:1 ratio of the two drugs is optimal and that a range of 27.3 g/ton (30 ppm) to 45.5 g/ton (50 ppm) of each narasin and nicarbazin is effective depending upon the severity of the coccidial challenge.

Effectiveness studies were conducted as follows:

A. Battery trials - A series of ninety-four battery trials to evaluate the anticoccidial dose response of a 1:1 combination of narasin and nicarbazin in broiler chicken rations.
B. Floor pen trials - A series of thirteen trials to evaluate the anticoccidial dose response of five levels of a 1:1 ratio of narasin and nicarbazin under simulated field conditions.

Experimental Results

B. Battery Trials

Ninety-four battery trials were conducted as dose response studies of a 1:1 combination of narasin and nicarbazin fed to broiler chickens. The chickens in each trial were inoculated with species of Eimeria as follows.

E. acerrulina	18
E. brunetti	3
E. maxima	9
E. mivati	4
E. necatrix	3
E. tenella	29
Mixed species with *E. tenella*	19
Mixed species without *E. tenella*	9

The results are presented in Tables 1 through 26. They provide a basis for the conclusion that narasin and nicarbazin is effective within the range of 27/27 to 45/45 g/ton for the prevention of mixed species Eimeria infections.

The investigator for this series of trials was:

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Lilly Research Laboratories
Greenfield, Indiana 46140

TABLE 1 *E. acerrulina*, INTESTINAL LESION SCORE MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C8301	3.95	3.50	2.05	1.05	0.05	1.87	0.08
09	3.95	2.86	1.40	0.71	0.20	0.13	3.60
10	3.90	3.12	2.15	0.80	0.15	0.53	3.87
30	3.65	2.75	1.71	0.55	0.65	1.27	0.37
31	4.00	3.40	1.70	1.60	1.10	2.47	0.95
32	3.85	2.30	2.18	1.41	0.91	0.80	3.27
52	1.40	0.40	0.65	0.22	0.06	0.17	0.67
53	1.55	1.16	0.60	0.42	0.10	0.17	1.13
75	3.55	2.10	1.45	0.45	0.10	1.32	0.00
79	3.90	1.00	0.00	0.00	0.00	0.00	0.00
80	3.85	0.78	0.05	0.00	0.00	0.20	0.00
81	3.90	0.80	0.25	0.15	0.00	0.00	0.00
86	3.54	2.90	1.60	0.65	0.15	1.80	0.13
91	4.00	2.80	1.70	0.50	0.05	1.27	0.33
98	3.65	2.60	2.50	0.35	0.55	1.13	2.75
B3	1.60	0.20	0.00	0.10	0.10	0.00	0.20
B4	2.96	1.62	0.64	0.45	0.00	1.29	0.69
B6	3.50	1.65	0.10	0.00	0.00	0.60	0.00
All Trials	3.37	2.00	1.15	0.52	0.23	0.83	1.00
Std. Error	0.16	0.16	0.16	0.16	0.16	0.19	0.19

Statistically effective range is 18/18 to 45/45.

63/0 is statistically better than 0/0
" 18/18
equal to 27/27
" 36/36
worse than 45/45

0/112 is statistically better than 0/0
" 18/18
equal to 27/27
worse than 36/36
" 45/45

TABLE 2 *E. acerrulina*, WEIGHT GAIN MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C8301	205.8	205.8	233.2	239.4	240.8	225.1	223.7
09	194.4	231.7	244.6	241.2	226.8	242.4	207.9
10	201.0	207.4	231.2	243.4	229.3	250.4	206.3
30	234.4	241.7	237.3	231.0	228.4	225.1	222.5
31	197.7	238.5	236.6	239.6	241.5	226.9	226.5
32	212.3	224.9	242.1	232.7	237.0	234.7	206.4
52	202.2	193.4	195.8	192.3	184.2	174.7	186.7
53	209.2	215.9	210.0	204.8	210.7	222.8	201.4
75	234.0	255.0	251.4	243.4	248.2	236.9	218.9
79	202.4	242.2	234.2	239.8	229.7	236.9	230.1
80	201.7	235.4	223.6	239.6	227.0	213.1	215.7
81	210.6	228.9	237.0	235.3	257.3	224.5	210.4
86	225.0	244.2	259.7	263.8	261.2	249.1	249.5
91	232.0	262.1	262.0	265.2	265.4	269.9	258.3
98	166.5	188.5	196.8	196.2	195.6	177.7	170.6
B3	235.2	249.6	259.8	258.8	265.1	276.1	246.7
B4	196.9	230.2	262.8	273.4	276.7	267.6	250.5
B6	226.4	267.1	283.1	274.0	287.2	267.7	251.9
All Trials	210.4	231.2	238.9	239.7	239.6	236.2	221.3
Std. Error	3.4	3.4	3.4	3.4	3.4	3.9	3.9

Statistically effective range is 18/18 to 27/27.

63/0 is statistically better than 0/0
equal to 18/18
" 27/27
" 36/36
" 45/45

0/112 is statistically better than 0/0
worse than 18/18
" 27/27
" 36/36
" 45/45

TABLE 3 *E. brunetti*, INTESTINAL LESION SCORE MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C8304	3.00	1.31	1.30	1.11	1.65	1.80	1.47
08	3.45	2.50	1.08	1.35	0.55	1.12	0.88
85	3.40	2.72	1.42	2.00	1.25	2.40	1.80
All Trials							
Std. Error							

Statistically effective range is 18/18 to 27/27.

63/0 is statistically better than 0/0
equal to 18/18
" 27/27
" 36/36
" 45/45

0/112 is statistically better than 0/0
" 18/18
equal to 27/27
" 36/36
" 45/45

TABLE 4 *E. brunetti*, WEIGHT GAIN MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C8304	175.9	278.9	279.0	274.5	260.6	249.1	256.9
08	147.7	217.2	216.6	237.4	217.1	243.6	240.2
85	162.0	266.3	279.3	272.8	271.2	233.2	254.8
All Trials	161.8	245.1	258.3	261.6	249.6	242.0	250.6
Std. Error	7.8	7.8	7.8	7.8	7.8	9.0	9.0

Statistically effective range is 18/18 to 29/29.

63/0 is statistically better than 0/0
equal to 18/18
" 27/27
" 36/36
" 45/45

0/112 is statistically better than 0/0
equal to 18/18
" 27/27
" 36/36
" 45/45

TABLE 5 *E. maxima*, INTESTINAL LESION SCORE MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C8302	3.70	3.40	2.10	2.04	1.00	3.27	1.42
34	3.95	1.15	1.02	0.10	0.15	1.38	0.60
35	4.00	2.69	1.05	0.50	0.00	2.07	0.25
36	4.00	1.30	0.35	0.15	0.00	2.08	0.33
37	4.00	2.42	1.28	0.91	0.50	2.92	1.23
72A	2.75	1.62	1.31	1.06	0.94	2.11	1.22
72B	3.00	2.14	1.84	1.16	1.14	1.97	1.81
72C	2.97	2.17	1.78	1.64	0.83	2.42	2.06
78	3.85	1.31	1.10	1.25	0.60	1.12	1.72
All Trials	3.58	2.02	1.31	0.98	0.57	2.15	1.18
Std. Error	0.16	0.16	0.16	0.16	0.16	0.18	0.18

Statistically effective range is 18/18 to 45/45.

63/0 is statistically better than 0/0
equal to 18/18
worse than 27/27
" 36/36
" 45/45

0/112 is statistically better than 0/0
" 18/18
equal to 27/27
" 36/36
worse than 45/45

TABLE 6 *E. maxima*, WEIGHT GAIN MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C8302	198.2	241.8	264.1	265.0	242.1	246.6	232.7
34	195.5	240.4	249.1	257.0	259.6	259.7	225.5
35	166.8	233.2	263.4	259.8	258.6	252.7	238.0
36	169.8	228.2	248.1	222.2	222.7	237.7	231.7
37	212.6	264.6	275.0	274.4	264.2	263.6	255.3
72A	261.3	266.0	257.1	258.6	275.4	257.0	263.0
72B	255.6	267.1	244.5	257.5	270.8	270.3	268.5
72C	212.0	216.3	258.3	259.3	230.5	220.2	233.2
78	178.1	249.4	257.0	255.4	252.1	228.3	214.3
All Trials	205.6	245.2	257.4	256.6	252.9	248.5	240.2
Std. Error	4.7	4.7	4.7	4.7	4.7	5.2	5.2

Statistically effective range is 18/18 to 31/31.

63/0	is statistically better	than 0/0	0/112	is statistically better	than 0/0
	equal to	18/18		equal to	18/18
	"	27/27		worse	than 27/27
	"	36/36		"	36/36
	"	45/45		equal to	45/45

TABLE 7 *E. mivati*, INTESTINAL LESION SCORE MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4HgC8312	3.70	2.15	1.99	1.75	1.55	2.07	2.13
71A	3.75	0.17	0.00	0.25	0.75	1.08	0.00
71B	3.67	0.58	0.25	0.08	0.42	0.67	0.00
71C	3.83	2.17	0.33	0.00	0.00	0.83	0.83
All Trials	3.74	1.27	0.64	0.52	0.68	1.16	0.74
Std. Error	0.26	0.26	0.26	0.26	0.26	0.27	0.27

Statistically effective range is 18/18 to 32/32.

63/0	is statistically better	than 0/0	0/112	is statistically better	than 0/0
	equal to	18/18		equal to	18/18
	"	27/27		"	27/27
	"	36/36		"	36/36
	"	45/45		"	45/45

TABLE 8 *E. mivati*, WEIGHT GAIN MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4HgC8312	128.2	128.8	150.6	160.6	167.7	159.1	120.7
71A	202.8	245.7	250.5	234.0	255.0	222.9	214.5
71B	196.6	212.8	256.4	249.1	249.8	233.4	234.5
71C	148.7	245.8	249.1	249.3	255.0	227.3	228.2
All Trials	169.1	208.3	226.7	223.3	231.9	210.7	199.5
Std. Error	8.0	8.0	8.0	8.0	8.0	8.2	8.2

Statistically effective range is 18/18 to 27/27.

63/0 is statistically better than 0/0
equal to 18/18
" 27/27
" 36/36
" 45/45

0/112 is statistically better than 0/0
equal to 18/18
worse than 27/27
" 36/36
" 45/45

TABLE 9 E. necatrix, INTESTINAL LESION SCORE MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C83C5	3.74	1.00	0.58	0.40	0.69	0.40	1.00
11	2.65	0.10	0.30	0.05	0.00	0.00	0.17
33	3.06	0.47	0.35	0.32	0.00	0.13	0.53
All Trials	3.15	0.52	0.41	0.26	0.23	0.18	0.57
Std. Error	0.12	0.12	0.12	0.12	0.12	0.14	0.14

Statistically effective range is 18/18 to 36/36.

63/0 is statistically better than 0/0
equal to 18/18
" 27/27
" 36/36
" 45/45

0/112 is statistically better than 0/0
equal to 18/18
" 27/27
" 36/36
" 45/45

TABLE 10 *E. necatrix*, WEIGHT GAIN MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C83C5	204.0	289.4	290.0	278.8	272.0	288.4	268.5
11	193.2	289.0	267.8	287.4	282.7	281.4	275.0
33	232.0	245.2	255.6	232.8	244.0	264.0	237.9
All Trials	209.7	274.5	272.1	266.3	266.2	277.9	260.5
Std. Error	9.7	10.2	9.7	9.7	9.7	11.2	11.2

Statistically effective range is 18/18.

63/0 is statistically better than 0/0
equal to 18/18
" 27/27
" 36/36
" 45/45

0/112 is statistically better than 0/0
equal to 18/18
" 27/27
" 36/36
" 45/45

TABLE 11 *E. tenella*, CECAL LESION SCORE MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C83AI	3.45	3.55	1.38	1.19	0.85	1.80	1.00
A2	4.00	3.80	3.25	2.51	2.45	3.73	1.73
A3	3.80	4.00	3.65	3.30	2.45	3.48	2.13
05	3.51	3.65	3.30	2.81	2.12	3.65	2.00
06	3.15	3.50	2.30	1.65	1.65	3.07	1.27
07	3.05	3.30	2.10	1.20	1.35	1.40	2.27
38	3.05	3.25	1.74	1.10	1.52	2.27	1.72
39	3.75	3.36	1.76	1.40	1.19	2.11	1.73
40	3.55	3.25	2.06	1.46	1.48	2.70	1.60
41	3.40	3.60	3.22	2.90	1.80	3.67	1.30
46	3.69	3.50	3.16	2.56	1.56	3.31	1.48
47	3.51	3.25	2.10	1.75	1.26	3.07	2.20
49	3.55	3.55	2.30	1.88	1.50	2.93	2.00
54	3.60	3.22	1.90	2.16	1.92	3.08	1.90
55	2.22	1.35	0.85	0.29	0.28	1.27	0.08
73B	1.33	3.17	1.00	0.50	0.42	1.83	0.83
73C	2.64	3.75	1.42	1.25	0.39	3.42	0.58
74A	2.08	3.25	0.92	0.83	0.75	2.67	0.33
74B	2.92	3.25	2.58	1.25	1.06	3.25	0.83
74C	3.42	3.58	2.75	2.50	2.00	3.67	1.67
76	3.46	3.11	2.94	1.72	1.30	2.93	1.67
77	3.58	3.06	2.98	1.36	1.15	3.23	1.73
82	3.45	3.31	3.49	1.94	1.63	3.40	1.00
83	3.33	2.41	2.25	0.85	0.70	1.67	1.50
84	3.50	1.71	1.50	0.40	0.20	1.20	0.67
94	3.80	3.52	2.75	1.55	1.60	3.27	1.28
95	3.70	3.50	3.45	2.78	2.55	3.57	1.55
97	3.65	3.52	2.65	1.70	1.85	3.33	1.87
99	2.55	0.91	1.02	0.55	0.35	1.67	0.40
All Trials	3.28	3.12	2.31	1.63	1.36	2.78	1.39
Std. Error	0.08	0.08	0.08	0.08	0.08	0.09	0.09

Statistically effective range is 27/27 to 40/40.

63/0 is statistically better than 0/0
" 18/18
worse than 27/27
" 36/36
" 45/45

0/112 is statistically better than 0/0
" 18/18
" 27/27
" 36/36
equal to 45/45

TABLE 12 *E. tenella*, WEIGHT GAIN MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C83AI	196.6	248.1	262.4	252.6	282.2	244.8	209.9
A2	134.7	187.0	250.0	263.3	244.8	222.3	246.1
A3	180.1	165.9	233.6	264.4	255.0	245.2	232.9
05	161.4	176.0	228.8	235.5	228.8	212.4	208.4
06	207.6	229.2	224.0	212.8	217.4	240.4	223.9
07	216.8	230.2	227.0	229.9	212.6	232.7	220.9
38	211.7	253.2	285.2	273.2	263.1	257.2	252.6
39	144.7	236.3	249.5	254.0	235.1	250.2	248.0
40	169.1	240.8	252.8	267.9	268.2	266.4	237.5
41	193.4	221.9	222.9	236.0	239.4	206.1	240.8
46	114.6	169.0	227.2	218.3	244.3	184.9	244.2
47	178.9	207.3	251.1	252.2	245.9	206.7	239.1
49	164.8	246.0	259.2	268.3	250.4	227.9	243.1
54	211.4	245.6	240.0	246.6	236.2	234.1	221.8
55	239.6	235.0	232.4	238.0	232.4	220.1	243.9
73B	298.7	284.4	300.8	297.4	295.9	277.4	275.0
73C	262.2	259.7	278.6	281.3	279.8	264.8	264.4
74A	293.3	272.5	272.0	308.9	314.4	293.8	295.8
74B	258.3	255.4	274.8	274.4	299.9	257.5	255.9
74C	240.5	167.2	271.0	256.7	247.5	162.2	229.4
76	203.4	256.3	249.7	269.6	258.1	233.7	255.5
77	169.4	215.1	200.8	247.0	219.4	217.8	209.9
82	214.9	272.5	260.3	277.0	281.0	246.9	265.0
83	206.9	266.5	273.2	285.7	276.6	272.6	258.2
84	183.6	257.5	262.3	268.1	266.8	266.7	252.7
94	167.6	233.7	251.4	274.6	262.2	240.8	273.4
95	201.1	240.0	261.0	271.3	258.6	239.4	260.4
97	168.4	267.3	260.2	266.8	278.0	236.3	248.1
99	238.6	242.8	229.4	231.5	202.2	219.1	200.1
All Trials	210.1	235.4	250.2	255.2	250.9	237.6	241.2
Std. Error	3.9	3.9	3.9	3.9	3.9	4.4	4.4

Statistically effective range is 18/18 to 27/27.

63/0 is statistically better than 0/0
equal to 18/18
worse than 27/27
" 36/36
" 45/45

0/112 is statistically better than 0/0
equal to 18/18
" 27/27
worse than 36/36
equal to 45/45

TABLE 13 MIXED WITH *E. tenella*, CECAL LESION SCORE MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C83A0	1.85	1.00	0.40	0.10	0.20	1.05	0.20
A4	2.82	3.90	2.79	1.75	1.00	3.20	0.87
A5	2.34	2.45	0.95	0.75	0.50	2.37	0.45
A7	3.04	3.11	2.70	1.80	0.85	3.08	0.20
A8	3.05	2.90	2.30	1.45	0.76	3.33	0.13
B7	3.15	2.84	1.80	0.75	0.44	2.67	0.47
B8	3.32	3.15	2.56	1.60	0.50	3.12	1.07
B9	3.46	2.84	2.40	1.90	0.80	2.33	0.67
CI	3.79	3.45	2.80	0.51	0.31	3.27	1.33
C3	3.31	3.43	2.20	0.99	1.00	3.17	0.07
C4	2.96	3.10	2.40	1.00	0.15	2.27	0.07
44	3.30	3.34	1.50	1.15	0.60	1.93	1.87
45	3.84	3.73	3.09	2.35	1.80	3.00	0.90
48	3.54	2.80	1.25	1.20	0.30	1.73	0.87
50	3.78	3.18	2.88	2.05	1.20	2.29	1.20
51	3.06	3.33	2.65	2.35	1.35	2.53	1.20
92	3.16	1.80	0.85	0.50	0.30	2.00	0.37
93	3.57	2.81	1.22	0.45	0.46	1.27	0.43
96	3.52	2.50	1.09	0.65	0.50	2.00	0.80
All Trials	3.20	2.93	1.99	1.23	0.68	2.45	0.69
Std. Error	0.10	0.10	0.10	0.10	0.10	0.11	0.11

Statistically effective range is 18/18 to 45/45.

63/0 is statistically better than 0/0
" 18/18
worse than 27/27
" 36/36
" 45/45

0/112 is statistically better than 0/0
" 18/18
" 27/27
" 36/36
equal to 45/45

TABLE 14 MIXED WITH *E. tenella*, INTESTINAL LESION SCORE MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C83A0	1.35	1.00	0.45	0.16	0.05	0.57	0.29
A4	1.89	1.75	0.88	0.55	0.23	2.17	0.22
A5	2.13	1.90	0.68	0.28	0.15	1.51	0.19
A7	2.82	2.38	1.19	0.55	0.20	2.39	0.18
A8	2.88	2.25	1.56	0.42	0.10	2.09	0.00
B7	2.52	2.27	1.77	1.15	0.16	2.15	1.00
B8	2.89	2.82	2.28	20.05	0.08	2.67	1.78
B9	2.85	2.28	1.93	1.57	1.03	1.75	1.93
CI	2.37	1.72	1.00	0.66	0.48	1.11	0.58
C3	2.49	1.93	0.55	0.29	0.14	1.27	0.20
C4	2.44	1.60	1.05	0.32	0.07	1.87	0.00
44	1.32	0.53	0.20	0.03	0.03	0.22	0.09
45	1.94	0.52	0.24	0.19	0.00	0.67	0.03
48	1.21	0.82	0.28	0.25	0.00	0.16	0.62
50	1.92	1.43	0.40	0.40	0.40	0.73	0.60
51	2.10	1.58	0.45	0.75	0.15	1.30	0.33
92	3.80	1.55	0.55	0.10	0.00	1.13	0.00
93	2.71	1.76	0.50	0.32	0.14	0.07	1.61
96	2.68	0.63	0.20	0.06	0.35	0.00	0.58
All Trials	2.33	1.62	0.85	0.53	0.18	1.26	0.54
Std. Error	0.12	0.12	0.12	0.12	0.12	0.14	0.14

Statistically effective range is 18/18 to 45/45.

63/0 is statistically better than 0/0
" 18/18
worse than 27/27
" 36/36
" 45/45

0/112 is statistically better than 0/0
" 18/18
equal to 27/27
" 36/36
worse than 45/45

TABLE 15 MIXED WITH *E. tenella*, WEIGHT GAIN MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C83A0	206.1	238.4	253.2	255.4	247.9	220.9	226.4
A4	146.8	171.6	232.0	249.2	253.2	185.3	242.4
A5	155.0	189.7	284.0	254.0	254.6	202.0	223.3
A7	225.0	253.0	298.8	294.3	306.3	249.6	296.7
A8	220.0	250.3	297.0	292.4	283.9	287.3	277.7
B7	189.4	273.8	276.6	270.8	295.3	255.6	266.7
B8	189.0	234.7	255.1	282.4	287.7	238.5	277.2
B9	203.1	247.3	264.2	268.8	274.6	238.1	269.7
CI	204.8	251.9	262.3	289.3	277.2	231.9	269.7
C3	204.6	245.3	275.0	290.5	288.4	234.4	278.4
C4	201.9	255.2	271.8	272.2	278.9	250.5	268.3
44	145.5	206.2	245.8	257.6	249.2	231.5	231.1
45	150.6	162.9	219.8	228.0	255.5	123.0	243.9
48	148.0	223.6	251.5	256.8	259.8	231.9	240.9
50	174.9	220.4	262.8	228.2	242.8	253.3	237.6
51	184.1	213.9	246.6	238.6	237.8	233.4	241.7
92	216.0	258.8	267.6	275.9	277.4	260.9	285.3
93	213.7	255.8	281.7	266.8	284.2	288.8	249.5
96	226.0	264.2	259.2	265.0	259.4	272.8	237.0
All Trials	189.6	234.1	261.0	265.1	270.5	235.4	258.3
Std. Error	3.2	3.2	3.2	3.2	3.2	3.7	3.7

Statistically effective range is 18/18 to 45/45.

63/0 is statistically better than 0/0
" equal to 18/18
" worse than 27/27
" " 36/36
" " 45/45

0/112 is statistically better than 0/0
" " 18/18
" equal to 27/27
" " 36/36
" worse than 45/45

TABLE 16 MIXED WITHOUT *E. tenella*, INTESTINAL LESION SCORE MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C8303	2.22	0.26	0.02	0.02	0.00	0.11	0.00
A9	2.64	1.18	1.08	0.94	0.41	1.22	0.82
B0	2.97	1.44	1.14	0.25	0.10	1.40	0.04
B1	2.35	1.40	0.68	0.23	0.28	1.65	0.40
B2	2.56	1.15	1.15	0.60	0.30	1.07	0.68
C0	2.70	1.53	0.62	0.62	0.38	1.07	1.03
C2	2.03	0.72	0.75	1.46	0.66	1.29	1.42
C6	2.60	1.54	0.90	0.43	0.34	1.29	1.71
C7	2.80	2.20	0.60	0.48	0.30	1.34	1.56
All Trials	2.54	1.27	0.77	0.56	0.31	1.16	0.85
Std. Error	0.14	0.14	0.14	0.14	0.14	0.16	0.16

Statistically effective range is 18/18 to 45/45.

63/0 is statistically better than 0/0
" equal to 18/18
" " 27/27
" worse than 36/36
" " 45/45

0/112 is statistically better than 0/0
" " 18/18
" equal to 27/27
" " 36/36
" worse than 45/45

TABLE 17 MIXED WITHOUT *E. tenella*, WEIGHT GAIN MEANS

	Narasin and Nicarbazin, g/ton						
Trial	**0/0**	**18/18**	**27/27**	**36/36**	**45/45**	**63/0**	**0/112**
T4H8C8303	179.3	261.5	261.0	260.1	145.2	236.8	246.5
A9	195.0	228.3	213.0	228.6	238.8	210.4	230.5
B0	229.4	275.1	290.6	296.4	304.8	273.3	285.9
B1	234.4	250.7	278.8	286.7	252.0	273.8	260.6
B2	276.0	276.4	291.4	299.3	283.2	289.5	261.2
C0	227.6	264.4	265.0	292.6	289.4	260.2	255.4
C2	234.0	240.0	267.8	274.6	260.8	262.5	267.1
C6	195.6	237.0	271.8	248.2	245.0	252.7	231.6
C7	226.0	281.8	283.5	297.4	294.8	276.2	276.4
All Trials	221.9	257.2	269.2	276.0	268.2	259.5	258.1
Std. Error	4.3	4.3	4.3	4.3	4.3	5.0	5.0

Statistically effective range is 18/18 to 33/33.

63/0 is statistically better than 0/0
" equal to 18/18
" " 27/27
" worse than 36/36
" equal to 45/45

0/112 is statistically better than 0/0
" equal to 18/18
" " 27/27
" worse than 36/36
" equal to 45/45

TABLE 18 *E. acervulina* SENSITIVE TO NARASIN AND NICARBAZIN TRIAL T2N8C8157

PART A. INTESTINAL LESION SCORE MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	3.65	3.00	1.18	0.30	0.00	0.00	0.00
18	3.80	0.80*	0.20	0.00	0.00	-	-
36	3.80	0.00*	0.05	0.00	0.00	-	-
54	0.90	0.00	0.00	0.00	-	-	-
72	0.20	0.00	0.00	-	-	-	-
90	0.00	0.00	-	-	-	-	-
108	0.00	-	-	-	-		-

Standard error is 0.12
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 18 *E. acervulina* SENSITIVE TO NARASIN AND NICARBAZIN TRIAL T2N8C8157

PART B. WEIGHT GAIN MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	143.3	203.3	215.6	232.4	223.7	215.1	205.1
18	166.1	226.2*	230.9*	215.6	229.6	210.0	-
36	193.4	228.3	223.4	213.4	225.0	-	-
54	203.5	220.9	218.5	204.2	-	-	-
72	218.8	204.8	214.1	-	-	-	-
90	219.2	204.2	-	-	-	-	-
108	208.5	-	-	-	-	-	-

Standard error is 14.2
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 19 *E. maxima* SENSITIVE TO NARASIN AND NICARBAZIN TRIALS T4H8C8205 and T4H8C8243

PART A. INTESTINAL LESION SCORE MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	3.71	3.37	1.79	1.40	0.57	0.22	0.09
18	3.79	1.02*	0.35*	0.15*	0.01*	0.11	-
36	3.41	0.40*	0.11*	0.05	0.07	-	-
54	2.33	0.13*	0.37	0.20	-	-	-
72	2.00	0.16	0.11	-	-	-	-
90	0.75	0.01	-	-	-	-	-
108	0.72	-	-	-	-	-	-

Standard error is 0.15
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 19 *E. maxima* SENSITIVE TO NARASIN AND NICARBAZIN TRIALS T4H8C8205 and T4H8C8243

PART B. WEIGHT GAIN MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	170.0	200.3	244.7	232.4	235.2	241.5	219.3
18	182.1	235.5*	244.7	248.2	245.0	232.1	-
36	196.1	237.5	246.2	245.5	235.0	-	-
54	221.9	236.2	240.6	240.6	-	-	-
72	224.1	235.0	232.8	-	-	-	-
90	222.8	222.0	-	-	-	-	-
108	234.1	-	-	-	-	-	-

Standard error is 5.7
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 20 *E. tenella* SENSITIVE TO NARASIN AND NICARBAZIN TRIAL T2N8C8152

PART A. CECAL LESION SCORE MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	3.60	3.35	1.95	1.65	1.15	1.20	0.85
18	3.40	2.00*	1.27*	1.17*	0.65*	1.05	-
36	3.65	1.50*	1.05*	0.85	0.65	-	-
54	2.00	1.65	1.25	1.00	-	-	-
72	2.06	1.22	1.05	-	-	-	-
90	1.60	1.10	-	-	-	-	-
108	1.40	-	-	-	-	-	-

Standard error is 0.20
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 20 E. tenella SENSITIVE TO NARASIN AND NICARBAZIN TRIAL T2N8C8152

PART B. WEIGHT GAIN MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	158.3	210.0	251.8	256.9	252.5	235.4	234.1
18	194.1	258.1*	252.9	260.1	249.9	225.8	-
36	225.9	246.9	253.7	243.8	235.9	-	-
54	244.3	257.9	255.8	243.7	-	-	-
72	236.7	239.5	231.9	-	-	-	-
90	244.5	249.0	-	-	-	-	-
108	242.9	-	-	-	-	-	-

Standard error is 8.3
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 21 *E. acerrulina* SENSITIVE TO NARASIN AND INSENSITIVE TO NICARBAZIN TRIALS T4H8C8159, T4H8C8244, and T4H8C8246

PART A. INTESTINAL LESION SCORE MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	3.83	3.28	1.96	1.35	0.72	0.32	0.23
18	3.70	2.66*	1.67	0.50*	0.32*	0.12	-
36	3.83	2.15*	0.96*	0.42	0.30	-	-
54	3.53	1.49*	0.79	0.18	-	-	-
72	3.27	1.33	0.42*	-	-	-	-
90	3.33	0.80*	-	-	-	-	-
108	3.37	-	-	-	-	-	-

Standard error is 0.21
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 21 *E. acerrulina* SENSITIVE TO NARASIN AND INSENSITIVE TO NICARBAZIN TRIALS T4H8C8159, T4H8C8244, and T4H8C8246

PART B. WEIGHT GAIN MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	153.8	172.2	196.7	192.4	188.3	188.8	182.4
18	161.5	193.0*	188.4	195.8	189.9	191.1	-
36	159.4	189.4	198.6	193.8	185.7	-	-
54	161.5	186.7	197.2	194.8	-	-	-
72	157.3	181.3	191.0	-	-	-	-
90	166.6	184.0	-	-	-	-	-
108	167.1	-	-	-	-	-	-

Standard error is 4.1
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 22 *E. tenella* SENSITIVE TO NARASIN AND INSENSITIVE TO NICARBAZIN TRIAL T4H8C8245

PART A. CECAL LESION SCORE MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	3.10	3.05	2.50	1.23	1.05	0.75	0.52
18	3.45	2.65*	1.60*	0.95	0.50*	0.60	-
36	3.05	1.60*	1.35*	0.75*	0.65	-	-
54	3.00	1.30*	1.10	0.90	-	-	-
72	2.87	0.95*	0.80	-	-	-	-
90	2.50	1.25	-	-	-	-	-
108	1.75	-	-	-	-	-	-

Standard error is 0.19
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 22 *E. tenella* SENSITIVE TO NARASIN AND INSENSITIVE TO NICARBAZIN TRIAL T4H8C8245

PART B. WEIGHT GAIN MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	204.3	222.3	251.5	270.8	271.4	266.5	244.1
18	212.9	258.3*	265.8	274.4	264.5	258.9	-
36	227.6	266.4*	262.8	266.3	260.1	-	-
54	237.9	270.8*	279.1*	270.4	-	-	-
72	239.4	261.3	250.7	-	-	-	-
90	244.0	256.1	-	-	-	-	-
108	255.0	-	-	-	-	-	-

Standard error is 8.2
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 23 *E. tenella* INSENSITIVE TO NARASIN AND SENSITIVE TO NICARBAZIN TRIALS T2N8C8153 and T4H8C8248

PART A. CECAL LESION SCORE MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	3.54	3.63	2.58	3.76	3.80	3.38	3.43
18	3.40	3.32	3.24	2.61*	1.88*	1.65*	-
36	3.08	1.88*	1.62*	1.25*	1.09*	-	-
54	1.48	1.28	1.23	0.88*	-	-	-
72	1.40	1.05	1.08	-	-	-	-
90	1.03	0.88	-	-	-	-	-
108	0.98	-	-	-	-	-	-

Standard error is 0.20
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 23 *E. tenella* INSENSITIVE TO NARASIN AND SENSITIVE TO NICARBAZIN TRIALS T2N8C8153 and T4H8C8248

PART B. WEIGHT GAIN MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	185.3	159.2	177.2	190.0	183.4	191.6	184.6
18	196.9	207.4	210.7*	226.6*	232.3*	227.6	-
36	228.4	238.8	238.1	233.3	245.5	-	-
54	240.2	232.2	231.9	225.9	-	-	-
72	234.9	231.9	227.6	-	-	-	-
90	227.8	233.9	-	-	-	-	-
108	220.9	-	-	-	-	-	-

Standard error is 6.4
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 24 *E. acerrulina* INSENSITIVE TO NARASIN AND NICARBAZIN TRIAL T4H8C8247

PART A. INTESTINAL LESION SCORE MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	4.00	3.90	3.55	3.10	2.40	1.33	1.10
18	3.75	3.65	2.75*	1.68*	1.23*	0.75*	-
36	3.60	2.20*	0.55*	0.15*	0.10	-	-
54	2.30	0.55*	0.33	0.00	-	-	-
72	1.45	0.38	0.00	-	-	-	-
90	1.60	0.35	-	-	-	-	-
108	0.88	-	-	-	-	-	-

Standard error is 0.23
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 24 *E. acerrulina* INSENSITIVE TO NARASIN AND NICARBAZIN TRIAL T4H8C8247

PART B. WEIGHT GAIN MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	161.4	186.0	174.0	179.4	197.9	195.0	182.0
18	172.6	193.6	214.6*	206.7	197.7	210.0	-
36	174.3	211.5*	221.9*	221.1	189.9	-	-
54	186.8	202.1	201.8	207.9	-	-	-
72	205.9	174.0	201.9	-	-	-	-
90	186.3	190.9	-	-	-	-	-
108	197.5	-	-	-	-	-	-

Standard error is 8.8
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 25 *E. maxima* INSENSITIVE TO NARASIN AND NICARBAZIN TRIAL T4H8C8160

PART A. INTESTINAL LESION SCORE.MEANS

Nicarbazin, g/ton	**Narasin, g/ton**						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	3.60	3.60	3.55	3.00	3.13	2.55	2.05
18	3.65	3.18*	3.07*	2.22*	2.02*	1.70*	-
36	3.80	2.55*	2.10*	1.65*	1.58	-	-
54	3.10	5.23*	1.35	0.95	-	-	-
72	3.00	1.35	1.10	-	-	-	-
90	2.70	0.92	-	-	-	-	-
108	2.15	-	-	-	-	-	-

Standard error is 0.23
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 25 *E. maxima* INSENSITIVE TO NARASIN AND NICARBAZIN TRIAL T4H8C8160

PART B. WEIGHT GAIN MEANS

Nicarbazin, g/ton	Narasin, g/ton						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	149.3	149.4	149.6	177.6	185.4	202.1	194.2
18	126.8	191.5*	209.9*	211.0*	225.9*	212.0	-
36	147.5	204.6*	212.9*	226.6*	224.3	-	-
54	178.4	225.1*	198.7	238.8	-	-	-
72	195.8	223.9	208.3	-	-	-	-
90	210.5	203.7	-	-	-	-	-
108	202.1	-	-	-	-	-	-

Standard error is 9.4
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 26 *E. tenella* INSENSITIVE TO NARASIN AND NICARBAZIN TRIAL T4H8C8249

PART A. CECAL LESION SCORE MEANS

Nicarbazin, g/ton	Narasin, g/ton						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	2.80	3.10	3.40	3.53	3.60	3.18	3.25
18	3.20	3.50	2.60*	2.25*	1.65*	1.50	-
36	3.00	2.43*	1.25*	1.08*	0.95	-	-
54	2.65	0.90*	1.15	0.80	-	-	-
72	2.45	0.88	0.63	-	-	-	-
90	2.40	0.70	-	-	-	-	-
108	1.70	-	-	-	-	-	-

Standard error is 0.24
* Minimal combinations statistically better than 0/0 and each drug alone.

TABLE 26 *E. tenella* INSENSITIVE TO NARASIN AND NICARBAZIN TRIAL T4H8C8249

PART B. WEIGHT GAIN MEANS

Nicarbazin, g/ton	Narasin, g/ton						
	0	**18**	**36**	**54**	**72**	**90**	**108**
0	200.5	217.8	186.1	188.1	204.6	194.5	206.0
18	183.9	222.4	242.3*	228.6	235.0	238.3	-
36	208.6	233.7	240.0	224.5	241.2	-	-
54	222.0	234.1	246.2	243.2	-	-	-
72	221.3	231.0	236.5	-	-	-	-
90	221.2	229.1	-	-	-	-	-
108	223.7	-	-	-	-	-	-

Standard error is 8.5
* Minimal combinations statistically better than 0/0 and each drug alone.

C. Floor Pen Studies

A series of 13 floor pen trials involving 216 pens of day-old broiler cockerels and 214 pens of day-old broiler pullets were used to evaluate the anticoccidial dose response of five levels of narasin and nicarbazin maintained in a 1:1 ratio. The trials were conducted in six geographical locations with approximately 35,656 birds from five broiler strains. Treatments evaluated were nonmedicated control and the continuous feeding of five combinations of narasin and nicarbazin at 8/8, 18/18, 27/27, 36/36, or 45/45 g/ton for 43 to 46 days, followed by a five day nonmedicated withdrawal period. On day 20, 21, 23 or 24 of the trials, additional litter containing oocysts of recent field isolates of Eimeria acerrulina, E. brunetti, E. maxima, E. mivati, E. necatrix, and E. tenella was distributed equally to all experimental pens. Six or seven days later approximately 10 percent of the birds in each pen were sacrificed and scored for coccidial lesions. Data from these 13 trials show a broad anticoccidial efficacy range of narasin and nicarbazin in a 1:1 ratio. These trials are summarized in the following table:

Main Effects	**Number Expt. Units**	**Mortality (%)**	**Average Weight (lbs.)**	**Feed/ Gain**	**28-day Total Lesion Scores**	
					Intestinal	**Cecal**
Anticoccidial agent Nonmedicated control	71	5.10	4.323	2.125	2.45	0.77
Narasin 8 g/ton and nicarbazin 8 g/ton	72	3.77	4.341	2.087	1.81	0.56
Narasin 18 g/ton and nicarbazin 18 g/ton	72	4.24	4.418	2.066	1.12	0.37
Narasin 27 g/ton and nicarbazin 27 g/ton	71	3.77	4.489	2.042	0.82	0.14
Narasin 36 g/ton and nicarbazin 36 g/ton	72	3.45	4.475	2.045	0.34	0.05
Narasin 45 g/ton and nicarbazin 45 g/ton	72	4.29	4.456	2.020	0.20	0.02
Sex						
Cockerels	216	4.85	4.784	2.044	0.97	0.30
Pullets	214	3.39	4.050	2.084	0.98	0.28

The intestinal (2.45) and cecal (.77) lesion scores of those birds receiving no anticoccidial treatment indicated the birds had been subjected to a moderate intestinal and a low cecal coccidial challenge.

Intestinal lesion scores were decreased at each incremental increase in the narasin and nicarbazin dose level. Cecal lesion scores also were decreased at each incremental increase until narasin and nicarbazin were each fed at 45/45 g/ton. All narasin and nicarbazin treatment combinations decreased percent mortality as

compared to the birds receiving no anticoccidial treatment (3.45 to 4.29 vs 5.10 percent).

Final weights of birds fed narasin and nicarbazin each at 27/27, 36/36, or 45/45 g/ton were heavier than those fed narasin and nicarbazin at 18/18 g/ton. These birds, in turn, weighed more than those fed narasin and nicarbazin at 8/8 g/ton or those birds which received neither compound. Each incremental increase in the narasin and nicarbazin combinations improved feed/gain ratios except between 27/27 and 36/36 g/ton. No adverse effects were observed in any of these trials.

Data from these 13 trials show an efficacy range of narasin and nicarbazin in a 1:1 ratio.

The investigators for this series of trials were as follows:

1. Ben F. Schlegel, D.V.M.
   314 Fairway Lane
   Fayetteville, AR 72701
   Trial numbers: T4H058201, T4H058204, T4H058209, and T4H058210 (Wheeler, Arkansas)
2. Dean L. Snyder, V.M.D.
   800 Weadley Road
   Radnor, PA 19087
   Trial numbers: T4H428202 and T4H428208 (New Brilaen, Pennsylvania)
   Trial number: T4H548205 (West Virginia University, Morgantown, West Virginia)
3. Elbert Day, PH.D. and Ben Dilworth, Ph.D.
   Mississippi State University
   Starkville, Mississippi
   Trial number: T4H288203
4. Peter L. Long, Ph.D.
   University of Georgia
   Athens, Georgia
   Trial number: T4H138206
5. Maurice E. Callender, M.S.
   Lilly Research Laboratories
   Greenfield, Indiana
   Trial number: T4H8C8254, T4H8C8255, T4H8C8268, and T4H8C8269

III. TARGET ANIMAL SAFETY

Narasin is approved (21 CFR § 558.630) for incorporation into the rations of broiler chickens at levels of 54-72 g/ton, NADA 118-980 (51 FR 29098, August 14, 1986). Nicarbazin is approved (21 CFR § 558.366) for feeding to broiler chickens at 113.5 g/ton, NADA 135-468 (50 FR 13562, April 5, 1985).

The present NADA contains data reflecting the effectiveness and safety of the combination of these drugs at lower levels of each (22.7-45.4 g/ton of each narasin and nicarbazin).

Animal safety studies were conducted as follows:

1. Floor Pen Studies

A series of three studies to evaluate the safety of feeding narasin and nicarbazin under simulated field conditions.

2. Field Studies
   A series of five trials under commercial use conditions.

A. Floor Pen Studies (No. 1)

An experiment was designed to evaluate the safety of feeding 1:1 combinations of narasin and nicarbazin to broiler cockerels and pullets under simulated use conditions. Using a complete randomized block design, twenty-one hundred and twenty newly hatched Hubbard x White Mountain broilers (1060 cockerels and 2060 pullets) were allotted randomly by sex to 40 floor pens of 53 birds each in a broiler house. Treatments were 0+0, 50+50, 62.5+62.5,150+150 and 250+250 ppm of narasin and nicarbazin, respectively, with four pens of each sex per treatment. Each pen was equipped with self feeders and a waterer. The treatments were fed *ad libitum* in crumbled feed during the first four weeks and in pelleted feed during the last four weeks of the trial. At the end of the seven-week medicated feeding period, medicated feed was replaced with nonmedicated feed and fed for five days. Three randomly preselected birds were removed from the experiment at four days and bled to provide blood samples for prothrombin time determinations. Five randomly preselected birds were removed from each pen at the termination of the treatment period. Blood was collected from these birds for clinical pathology. They were then sacrificed for post-mortem examination and collection of preselected tissues for histopathology. Weight gain, feed consumption and feed gain ratios were determined at four and seven weeks and after a five-day withdrawal period. Mortality was recorded daily.

There were no treatment-related changes for any of the clinical pathology, growth performance or mortality variables at the two low treatments of 50+50 or 62.5+62.5 ppm of the combination. However, there were adverse dose-associated changes for some of the clinical pathology, growth performance and mortality variables for the two highest doses of 150+150 and 250+250 ppm of the combination. The most important finding in this study was congestive heart failure characterized by dilated cardiac chambers, fluid accumulation in body cavities and tissues, pulmonary and hepatic congestion and hepatic degeneration or necrosis. Congestive heart failure also occurred in seven chickens of the two lowest dose groups, but was not associated with increased total mortality. The incidence of congestive heart failure was associated with increased mortality in the two highest dose groups and was both dose and sex related. Mortality was greater for the two highest doses and greater in males than in females. Congestive heart failure was noted in four males and one female on the 50+50 ppm narasin and nicarbazin combination dose and in two male birds on the 62.5+62.5 ppm narasin and nicarbazin combination dose.

The low incidence of heart failure (1.25% and 0.5%) observed in the two low dose groups was not clearly treatment-related because it was not associated with increased total mortality and because similar effects in broiler chickens have previously been attributed to a variety of causes.(Julian, R.J. and Wilson, J.B. (1984), Ascites in broiler chickens caused by high levels of carbon monoxide. Proc. 56th Northeastern Conference on Avian Diseases. Pennsylvania State University, University Park. June 20-22, 1984)

The investigator for this study was:

Meliton N. Novilia, D.V.M., Ph.D.
Lilly Research Laboratories
Greenfield, Indiana 46140

B. Floor Pen Studies (Nos. 2 & 3)

TWO-MONTH SAFETY EVALUATION STUDIES WITH NARASIN AND NICARBAZIN IN BROILER CHICKENS

Study T4HVX8406 and T4HVX8407
Two time-replicated studies were conducted during the summer with Hubbard x White Mountain broiler chickens maintained on feed containing narasin and nicarbazin or narasin or nicarbazin alone as follows.

Treatment Group	Dose (ppm)		# of Pens	Number of Cockerels/Pen	Total Number Birds/ Treatment Group
	Narasin	Nicarbazin			
0	0	0	2	150	300
1	50	50	2	150	300
2	62.5	62.5	2	150	300
3	150	150	2	150	300
4	250	250	2	150	300
5	80	0	2	150	300
6	0	125	2	150	300
				TOTAL	2100

In each study, 2100 one-day-old cockerels were randomly distributed to 14 concrete floor pens of 150 birds each in a facility modified for floor pens studies. All pens were equipped with gas-fired brooders, self-feeders and automatic waterers. Feed was crumbled during the first four weeks of the study and pelleted during the last three weeks. The study duration was 49 days on medicated feed followed by a five-day withdrawal from medication.

Each pen was inspected twice a day for dead or moribund birds; these were weighed and submitted for necropsy. Other birds were observed for physical signs of toxicity. Growth performance data (weight gain, feed consumption, and feed/gain ratio) were determined at four weeks, seven weeks and at the end of a five-day withdrawal period. At the termination of the medication period, randomly preselected birds per pen were killed for necropsy. Tissues from all major organ systems were examined grossly and microscopically.

Pooled data for the seven-week treatment plus five-day withdrawal period indicated that mean mortality was increased in chickens fed 0 + 125 and 250 + 250 ppm narasin + nicarbazin. Increased mortality in the 0 + 125 ppm (narasin nicarbazin) treatment groups was episodic and was related to periodic elevations of ambient temperature. However, heat stress-related mortality did not occur with the 1:1 combination of up to 150 ppm each of narasin and nicarbazin. Mortality for the 80 + 0, 50 + 50, 62.5 + 62.5 and 150 + 150 ppm (narasin + nicarbazin) was similar to that of the control groups. No clinical signs of toxicity were observed although birds on 0 + 125 and 250 + 250 ppm narasin + nicarbazin were smaller than controls and

birds from the other treatment groups. Changes in growth performance variables were considered to be due to treatment-associated decreased feed consumption. Adverse findings, confined to the top two levels of 150 + 150 and 250 + 250 ppm narasin + nicarbazin, included decreased weight gain, reduced feed consumption and increased feed/gain ratio. Lower weight gain and feed consumption also occurred in the 0 + 125 ppm narasin + nicarbazin group. There was a treatment-related increase in the incidence and severity of congestive heart failure, myocardial degeneration and skeletal muscle degeneration and regeneration in birds given 150 + 150 and 250 + 250 ppm narasin + nicarbazin.

In conclusion, broiler chickens fed rations containing 1:1 combinations of up to 250 ppm each of narasin and nicarbazin for seven weeks with a five-day withdrawal from medication manifested adverse effects only to the top two levels of 150 + 150 and 250 + 250 ppm narasin + nicarbazin. These included growth depression, reduced feed efficiency, increased incidence of congestive heart failure and other cardiac skeletal muscle alterations, and increased mortality. Heat stress-related mortality which occurred in birds given nicarbazin alone at 125 ppm did not occur in groups given equal amounts of narasin and nicarbazin up to 150 ppm. There were no adverse findings in birds fed 80 + 0, 50 + 50, or 62.5 + 62.5 ppm narasin + nicarbazin.

C. Field Studies

Five field studies were conducted under commercial use conditions to evaluate the safety of the combination of narasin and nicarbazin. No adverse reactions were noted.

1. T4H378402

   Twenty-eight thousand four hundred eighteen straight run day-old Kennebec x Kennebec broiler chicks were allotted at random to two commercial broiler houses. For 43 days, narasin and nicarbazin each at 27.2 g/t (30 ppm) were fed to broilers in House 1 and narasin and nicarbazin each at 45.4 g/t (50 ppm) were fed to broilers in House 2. Both houses of birds were then placed on nonmedicated withdrawal feed four days prior to slaughter.

Treatment	Number Broilers Started	Age (days)	Weight (lbs)	Average Feed/ Gain	Mortality%
Narasin 27.2 g/t and nicarbazin 27.2 g/t	14,209	47	4.085	1.969	5.99
Narasin 45.4 g/t and nicarbazin 45.4 g/t	14,209	47	4.082	1.960	5.71

   There were no adverse reactions attributable to either treatment.

2. T4H488408

Twenty-five thousand straight run Peterson x Arbor Acre broiler chicks were allotted at random to two commercial broiler houses. For 49 days, narasin and nicarbazin each at 27.2 g/t (30 ppm) were fed to broilers in House 1 and narasin and nicarbazin each at 45.4 g/t (50 ppm) were fed to broilers in House 2. Both houses of birds were then placed on nonmedicated withdrawal feed four days prior to slaughter.

Treatment	Number Broilers Started	Age (days)	Weight (lbs)	Average Feed/ Gain	Mortality%
Narasin 27.2 g/t and nicarbazin 27.2 g/t	12,500	53	4.721	2.093	4.27
Narasin 45.4 g/t and nicarbazin 45.4 g/t	12,500	53	4.580	2.152	4.55

There were no adverse reactions attributable to either treatment.

3. T4H138409

Twenty thousand day-old Arbor Acre x Peterson broiler chicks from two breeder blocks were allotted to each of two 20,000 capacity commercial broiler houses. For 43 days, narasin and nicarbazin each at 27.2 g/t (30 ppm) were fed to broilers in House 2 and narasin and nicarbazin each at 45.4 g/t (50 ppm) were fed to broilers in House 3. Both houses of birds were then placed on nonmedicated withdrawal feed four days prior to slaughter.

Treatment	Number Broilers Started	Age (days)	Weight (lbs)	Average Feed/ Gain	Mortality%
Narasin 27.2 g/t and nicarbazin 27.2 g/t	20,000	48	3.750	2.030	2.930
Narasin 45.4 g/t and nicarbazin 45.4 g/t	20,000	48	3.837	2.028	2.990

There were no adverse reactions attributable to either treatment.

4. T4H288404

Twenty-one thousand straight run day-old broiler chicks were allotted at random to two commercial broiler houses. Arbor Acre x Petersen and Arbor Acre x Ross strains were used an were divided equally between treatments. For 44 days, narasin and nicarbazin each at 27.2 g/t (30 ppm) were fed to

broilers in House 1 and narasin and nicarbazin each at 45.4 g/t (50 ppm) were fed to broilers in House 2. Both houses of birds were then placed on nonmedicated withdrawal feed four days prior to slaughter.

Treatment	Number Broilers Started	Age (days)	Weight (lbs)	Average Feed/ Gain	Mortality %
Narasin 27.2 g/t and nicarbazin 27.2 g/t	12,500	53	4.721	2.093	4.27
Narasin 27.2 g/t and nicarbazin 27.2 g/t	10,500	48	4.150	2.016	3.70
Narasin 45.4 g/t and nicarbazin 45.4 g/t	10,500	48	3.921	2.092	5.18

There were no adverse reactions attributable to either treatment.

5. T4H288405

Twenty-one thousand straight run day-old broiler chicks were allotted at random to two commercial broiler houses. Arbor Acre x Arbor Acre strains were used. For 44 days, narasin and nicarbazin each at 27.2 g/t (30 ppm) were fed to broilers in House 3 and narasin and nicarbazin each at 45.4 g/t (50 ppm) were fed to broilers in House 4. Both houses of birds were then placed on nonmedicated withdrawal feed four days prior to slaughter.

Treatment	Number Broilers Started	Age (days)	Weight (lbs)	Average Feed/ Gain	Mortality %
Narasin 27.2 g/t and nicarbazin 27.2 g/t	10,500	48	4.097	2.049	4.81
Narasin 45.4 g/t and nicarbazin 45.4 g/t	10,500	48	4.135	2.034	4.16

There were no adverse reactions attributable to either treatment.

The investigators for this series of studies were:

L. Jerry Camp, D.V.M. - T4H378402
Jerome D. Yates, Ph.D. - T4H488408
James Brown - T4H138409
Jack Mullen - T4H288404
Jack Mullen - T4H288405

IV. HUMAN FOOD SAFETY

Both narasin and nicarbazin are approved new animal drugs. See Freedom of Information summaries for NADA 118-980 (51 FR 29098, August 14, 1986) and

NADA 135-468 (50 FR 13562, April 5, 1985). A tolerance for narasin residues in chickens is not needed, 21 CFR 556.428. The safe concentration for total narasin residues in uncooked edible chicken tissues are 0.6 ppm in muscle, 1.8 ppm in liver and 1.2 ppm in skin with adhering fat. A tolerance of 4 parts per million is established for residues of nicarbazin in uncooked chicken muscle, liver, and skin.

The following tissue residue study was conducted to evaluate drug decline in target tissues from broiler chickens fed a ration containing 45.4 g/ton each narasin and nicarbazin for eight weeks. Muscle, liver and skin/fat tissue samples were analyzed from chickens sacrificed after 0, 1, 2, 3 and 4 days withdrawal from medicated rations. Narasin tissue residue levels ranged from <5.0 ppb in muscle and liver to 30.5 ppb in skin/fat at 0 day withdrawal. No detectable residues of narasin in muscle, liver or skin/fat were found at 2 days withdrawal. Nicarbazin tissue residue levels ranged from <2.0 ppm in muscle and skin/fat to 7.6 ppm in liver at 0 day withdrawal as shown in the Summary Table. No detectable residue of nicarbazin in muscle and skin/fat, and <2.0 ppm residue in liver were found at 2 days withdrawal.

This study demonstrated that residues of each drug in the combination depleted below its safe concentration or tolerance by the proposed withdrawal period of 5 days.

Assay interference data were obtained from normal tissues fortified with each drug, with and without the presence of the second drug. Two hundred and fifty parts per billion (ppb) of narasin did not interfere with the assay of nicarbazin in tissues and 4.15 parts per million (ppm) of nicarbazin did not interfere with the assay of narasin in tissues.

SUMMARY TABLE TISSUE RESIDUE DATA* ON MEDICATED CHICKENS

Withdrawal Day	Muscle Tissue		Liver Tissue		Skin/Fat Tissue	
	Narasin ppb	Nicarbazin ppm	Narasin ppb	Nicarbazin ppm	Narasin ppb	Nicarbazin ppm
0	<5.0	<2.0	<5.0	7.6	30.5	<2.0
1	NDR**	NDR	NDR	4.0	8.4	<2.0
2	NDR	NDR	NDR	<2.0	NDR	
3	---	---	---	NDR	NDR	---
4	NDR	NDR	NDR	NDR	NDR	

* Residue values represent an average of 12 assays, duplicate assays on 3 composite samples per sex.
** NDR - no detectable residue with a limit of quantification of 2.0 ppm nicarbazin and 5 ppb narasin.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Act and demonstrate that narasin and nicarbazin at concentrations ranging from 27/27 g/ton to 45/45 g/ton of each in finished feeds are safe and effective when fed to broiler chickens for the indications stated on the product labeling.

A tolerance for narasin residues in chickens is not needed, 21 CFR 556.428. The safe concentration for total narasin residues in uncooked edible chicken tissues are 0.6 ppm in muscle, 1.8 ppm in liver and 1.2 ppm in skin with adhering fat. A tolerance of

4 parts per million is established for residues of nicarbazin in uncooked chicken muscle, liver, and skin. The tissue residue study submitted demonstrated that residues of each drug in combination depleted below its safe concentration by the proposed withdrawal period of five (5) days.

Adequate directions for use of Maxiban in broiler chickens has been written for the requested claims of this NADA. Products containing narasin and nicarbazin alone are currently available over-the-counter, therefore the Agency has concluded that approval of the combination (narasin and nicarbazin) will not significantly increase human exposure to residues of Maxiban in edible tissues.

VI. ATTACHMENTS

1. Blue Bird Medicated Article package label
2. Maxiban 72 Type A Medicated Article package label

Copies of these labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

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